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Population Pharmacokinetics of Ganciclovir in Newborns with Congenital Cytomegalovirus Infections

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The population pharmacokinetics of ganciclovir was investigated in a group of 27 newborns with symptomatic congenital cytomegalovirus infection by nonlinear mixed-effects modeling analysis. Individual characteristics including approximated creatinine clearance from serum (ASCC) and body weight (WGE) were identified to significantly influence total clearance from plasma (CL) and the apparent total volume of distribution (V) of ganciclovir, respectively. The regression equations used to model these relationships were expressed as CL (in liters per hour) = 0.262 + (0.00271 × ASCC) and V (in liters) = 0.627 + (0.437 × WGE). By using this model, typical values of the pharmacokinetic parameter CL and V were 0.428 ± 0.079 liters/h and 1.773 ± 0.320 liters, respectively. Upon validation with a larger number of newborns, this model should allow for the definition of possible relationships between the pharmacokinetic disposition of ganciclovir and pharmacodynamic events in neonates.

Ganciclovir is an acyclic nucleoside analog of guanine. This compound exhibits antiviral activity against human herpesviruses at relatively low inhibitory concentrations (5, 12, 13, 20). It has been approved as a first-line treatment for life- and/or sight-threatening cytomegalovirus (CMV) infections in high-risk immunocompromised patients (4, 14). Despite therapeutic efficacy, drug administration results in dose-dependent neutropenia and thrombocytopenia which require either the administration of granulocyte colony-stimulating factor or the partial interruption or discontinuation of therapy (2, 3, 8, 9, 16). The pharmacokinetic disposition of ganciclovir has been investigated in adults with normal and impaired renal function, CMV retinitis, or CMV pneumonitis and in newborns with congenital CMV infection (6, 18, 19, 21, 22). Those studies have demonstrated that despite dose-independent kinetics, large interpatient variability in fundamental pharmacokinetic parameters such as total clearance from plasma (CL) and apparent total volume of distribution (V) are found for ganciclovir. Since ganciclovir is excreted unchanged in the urine, it was hypothesized that CL correlates with creatinine clearance from serum (SCC) (6, 11, 18). Indeed, patients with impaired renal function have significantly reduced CL compared with the CL for patients with normal renal function (18). Empirical relationships determined by simple linear regression analyses correlating ganciclovir CL to SCC have been established (18). During the preparation of this report, the population pharmacokinetics of ganciclovir were reported in adult patients with CMV infections, with the demonstration that V is a linear function of body weight (WGE), and CL was expressed as a function of both WGE and SCC (23). No systematic population pharmacokinetic study with a pediatric population has yet been reported. In this report, ganciclovir pharmacokinetics were evaluated by nonlinear mixed-effects modeling analyses to define the population pharmacokinetic parameters (CL and V) for ganciclovir and to identify covariates influencing its kinetic disposition in newborns with congenital CMV infections.

After informed consent was obtained, 27 newborns with acute symptomatic CMV disease were enrolled in an open phase I-II trial designed to determine the pharmacokinetics, safety, and tolerance of ganciclovir as a 1-h intravenous infusion in a single dose of either 4 or 6 mg/kg of body weight. A total of 219 plasma samples were collected during and up to 12 h postinfusion, and drug levels were determined by a previously reported high-performance liquid chromatographic method characterized by a linear range of the calibration curve of from 0.1 to 5 μg/ml, a limit of quantitation of 0.1 μg/ml, and intra- and interassay coefficients of variation approximating 2 and 10%, respectively (17).

Pharmacostatistical modeling was performed with the nonlinear mixed-effects modeling program NONMEM (1). A one-compartment pharmacokinetic model with zero-order input and first-order elimination was used, with CL (in liters per hour) and V (in liters) being the basic parameters. Intersubject variabilities in CL and V, as well as residual variability, were assessed by proportional error models. The construction of the regression model for fixed effects consists of the following four steps: (i) fitting the basic model to the data to estimate global population mean values of CL and V and to obtain a reference value of −2 log likelihood (LLD); the difference between the −2 log LLD of the reduced and the full models is asymptotically χ^2 distributed; (ii) screening the influence of covariates on CL and V; (iii) constructing a full model incorporating the fixed effects which significantly improved the goodness-of-fit

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TABLE 1. Basic model estimates of ganciclovir population pharmacokinetic parameters for newborns[a]

Parameter	Parameter estimates	CV (%)
θ_{CL} (liter/h)	0.422	8.9
θ_V (liter)	1.64	7.6
ω^2_{CL}	0.183	20.6
ω^2_V	0.154	32.3
$\omega^2_{CL,V}$	0.109	40.0
σ^2	0.07	25.0

[a] CV, standard error of estimated θs expressed as coefficient of variation; θ_{CL}, structural parameter representing CL; θ_V, structural parameter representing V; ω^2, variance-covariance of random interindividual variability of the parameters; σ^2; variance of residual variability. The value of −2 log LLD was 251.0.

TABLE 2. Final model estimates of ganciclovir population pharmacokinetic parameters for newborns[a]

Parameter	Parameter estimates	CV (%)
CL (liter/h)		
θ_1	0.262	19.1
θ_2	0.00271	25.5
V (liter)		
θ_4	0.627	36.8
θ_5	0.437	26.8
ω^2_{CL}	0.125	26.7
ω^2_V	0.0904	39.9
$\omega^2_{CL,VD}$	0.0813	33.8
σ^2	0.00715	25.9

[a] See footnote *a* of Table 1 and text for definitions of the abbreviations. The value of −2 log LLD was 217.6.

($P < 0.001$); and (iv) refining a final model by removing covariates which, when set to their null value, failed to significantly increase the −2 log LLD value ($P > 0.005$).

The pharmacokinetics of ganciclovir in the plasma of newborns following short-term infusion was best described by a one-compartment model (21), being different from the biexponential pattern observed in adults (23). By fitting this basic model to levels of ganciclovir in plasma, a set of global population pharmacokinetic parameters was generated. The typical values for CL and V were 0.429 liters/h and 1.62 liters, respectively (Table 1). Thirteen covariates were evaluated for their effects on CL and V according to linear or categorical relationships. For CL, 11 covariates failed to significantly influence the parameters ($P > 0.001$). For V, 12 covariates did not significantly improve the goodness-of-fit. Among them, the factor dose level caused a drop in the −2 log LLD value of only 0.8 and 1.3 units when it was incorporated into CL and V models, respectively, indicating the kinetic linearity within the dose range studied. These factors were therefore not considered further. In contrast, two covariates (approximated SCC [ASCC; in milliliters per minute per 1.73 m^2] and platelet count (PLAT; in milliliters^{-3}) for the CL model and one (WGE) for the V model markedly improved the fit, as demonstrated by a highly significant ($P < 0.001$) drop in the −2 log LLD value. These factors were included in the full model. This model involved nine parameters, including five for the structural model and four for variability: $CL = \theta_1 + (\theta_2 \times ASCC) + (\theta_3 \times PLAT)$ and $V = \theta_4 + (\theta_5 \times WGE)$, where θ_1 to θ_5 are structural parameters. Of the three covariates, PLAT for the V model could be deleted from the full model because of a statistically insufficient ($P > 0.005$) increase in the −2 log LLD value when θ_3 was set equal to 0. This step led to the final model: $CL = \theta_1 + (\theta_2 \times ASCC)$ and $V = \theta_4 + (\theta_5 \times WGE)$., where θ_1 is equal to 0.262, θ_2 is equal to 0.00271, θ_4 is equal to 0.627, and θ_5 is equal to 0.437 (Table 2). Pharmacokinetic parameters (CL and V) obtained from the final model (mean ± standard deviation; CL = 0.428 ± 0.079 liter/h or 0.172 ± 0.045 liter/h/kg; V = 1.773 ± 0.320 liters or 0.694 ± 0.069 liter/kg) were in good accordance with those estimated individually (CL = 0.189 ± 0.028 liters/h/kg and V = 0.669 ± 0.070 liter/kg at 4 mg/kg, and CL = 0.213 ± 0.021 liter/h/kg and V = 0.749 ± 0.059 liter/kg at 6 mg/kg) (21). The ability of the final model to explain the interindividual variability in pharmacokinetic parameters was further assessed graphically by plotting post-hoc Bayesian estimates of CL and V from both the basic and final models versus the covariates. As shown in Fig. 1, the dependence of CL on ASCC and V on WGE, as was the case for the estimates obtained with the basic model, largely dropped after incorporation of the covariates into the final model. The influence of ASCC and WGE on the kinetics in plasma of ganciclovir administered at 4 mg/kg by a 1-h constant rate infusion was evaluated by simulation with the final model. Figure 2A illustrates the kinetics for two groups of newborns (200 newborns per group) with the same weight (3.5 kg; V = 2.162 ± 0.673 liters) but with different renal functions (ASCC = 27.5 and 143.0 ml/min/1.73 m^2 as the low and high bounds for the population studied, respectively). The results of these simulation studies demonstrated that a reduced ASCC leads to a low CL (0.344 ± 0.133 liters/h with a low ASCC compared with 0.665 ± 0.257 liter/h with a high ASCC), which resulted in enhanced levels of drug in plasma and a prolonged half-life (4.59 ± 1.11 h compared with 2.37 ± 0.57 h, respectively). Similarly, Fig. 2B illustrates the disposition of ganciclovir in plasma for two simulated groups of neonates (200 per group) with the same renal function (median value for the population, 50.6 ml/min/1.73 m^2, leading to CL = 0.408 ± 0.158 liter/h) but different weights (1.56 and 4.46 kg for the low and high bounds of the population studied, respectively). The simulation results indicated that a low weight representing a small V (1.312 ± 0.409 liters at 1.56 kg compared with 2.582 ± 0.804 liters at 4.46 kg) resulted in a decreased half-life (2.35 ± 0.57 compared with 4.62 ± 1.11 h, respectively).

Significant intersubject variabilities in pharmacokinetic parameters have prompted investigations to individualize treatment regimens for drugs with narrow therapeutic indices or for patients such as newborns with reduced hepatic and renal functions, or both. Traditional pharmacokinetic analyses provide precise estimates of individual parameters but necessitate a substantial number of biological samples per subject. These approaches also fail to consider potential pharmacokinetic-pharmacodynamic interactions, i.e., the relationships between pharmacokinetic parameters and individual characteristics (physical, physiological, and pathological factors). Some of these factors such as weight, age, and SCC have been shown to be frequently associated with interindividual variations in CL and V. A promising method for individualizing the dosing protocol is to identify the most dominant covariates implemented through nonlinear mixed-effects modeling analyses.

The glomerular filtration rate (GFR), as characterized by SCC, has been widely reported to be a key factor influencing the clearance of drugs with large urinary excretion rates. Different methods have been developed to estimate SCC on the basis of the serum creatinine level and body size (height and weight) and age. Among various approaches, Schwartz's formula, SCC (in milliliters per minute per 1.73 m^2) = (0.55 × height [in centimeters])/serum creatinine level (in milligrams

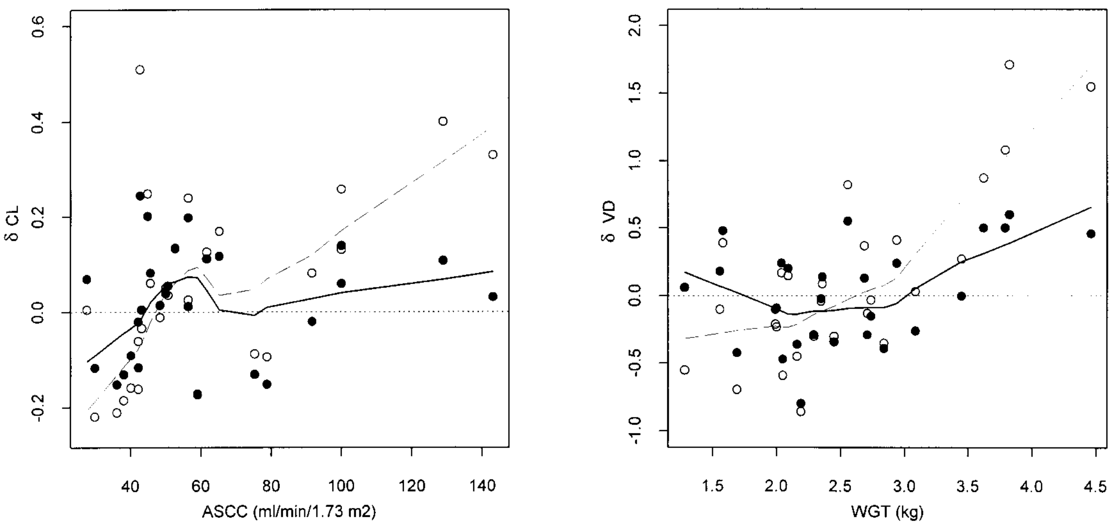

FIG. 1. Scatterplots of δCL versus ASSC and δV versus WGE from the basic model (○) and the final model (●), where δCL and δV are the differences between post-hoc Bayesian individual estimates of CL and V and their typical population values, respectively. The solid and dashed lines represent LOWESS smoothed curves of the scatterplot data for the final and the basic models, respectively.

per 100 ml), has provided adequate results for children as well as neonatal infants with postnatal ages ranging from 1 to 30 days (15, 24). While a detailed discussion on how SCC should be estimated is beyond the scope of the present report, it is of particular note that there is not an effective method for providing an accurate estimate of SCC for a pediatric intensive care population. The formula-derived SCC consistently overestimates GFR, particularly when the latter is below 40 ml/min/1.73 m^2 (7). Nevertheless, a positive and statistically significant correlation always exists between the formula-estimated SCC and the experimental value obtained with urine specimens collected from the subject (7, 10). In that context, we have, rather, considered the ASCC as another parameter that is indicative of renal function and that is also relative to SCC, but that is not an estimate of SCC itself. The equations of the final model indicate that ganciclovir CL increases linearly with increasing ASCC, being consistent with the findings for adults (6, 11, 18, 23). Although a possible correlation (r = 0.413; P = 0.032) between age and CL was previously suggested by pharmacokinetic analyses of individual data (21), this covariate did not provide a highly significant improvement in the goodness-of-fit (P = 0.01) and was deleted during the screening step. Concerning V, as expected, this parameter is a linear function of WGE, confirming information presented in our previous report (21) and recently published data on the population pharmacokinetics of the drug in adults (23). Another important feature revealed by the nonlinear mixed-effects modeling analyses during the screening step was a relationship between CL and PLAT. This covariate, when linearly entered into the CL model, significantly improved the goodness-of-fit, as evidenced by a drop of 12.6 units in the -2 log LLD value ($P < 0.001$). Since PLAT was assessed prior to ganciclovir administration,

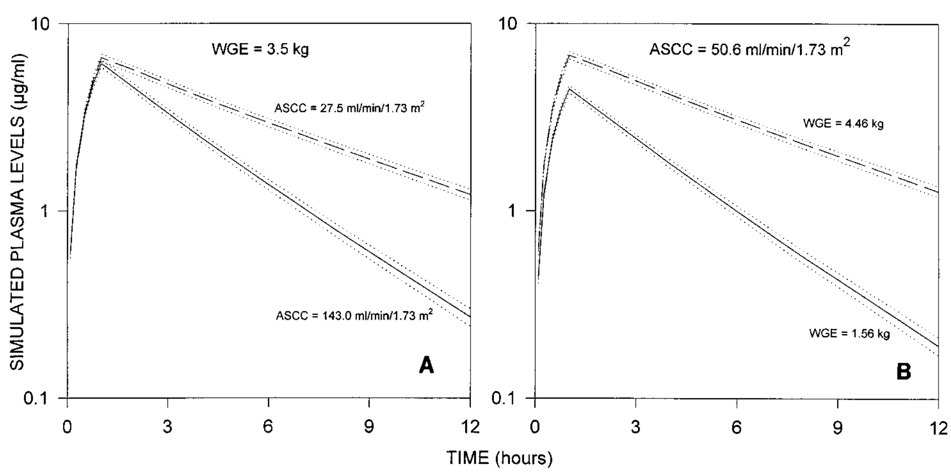

FIG. 2. Final model-simulated kinetics of ganciclovir in plasma administered at 4 mg/kg by 1-h intravenous infusions. The simulations were performed by using the NONMEM program, with the final model estimates including variance-covariance matrixes. Each curve represents the mean for 200 simulated individuals. Dotted lines are the 95% confidence interval outlines of the kinetics. (A) Influence of renal function on kinetics in plasma (solid and dashed lines represent kinetics simulated for newborns with high and low values of the approximated SCC, respectively); (B) influence of body weight on kinetics in plasma (solid and dashed lines represent kinetics simulated for newborns with low and high weights, respectively).

this covariate may also be considered, like SCC and WGE, a source of interindividual variability of the pharmacokinetics of ganciclovir. Moreover, this hematological value may be a reflection of disease progression, with the numbers of platelets varying with the disease severity. The origin of the observed correlation between PLAT and CL is unclear. This apparent relationship should be further investigated in a pharmacodynamic study which addresses relationships between pharmacokinetic parameters, virological markers, and clinical outcome during ganciclovir treatment.

In conclusion, by using stepwise nonlinear mixed-effects modeling analysis, we successfully identified the individual characteristics which largely account for the interindividual variabilities in the pharmacokinetics of ganciclovir in newborns. Characterization of quantitative relationships between the pharmacokinetic parameters and the covariates should allow for, with the availability of more virological and clinical endpoints from studies with a large number of newborns, further investigations on the possible pharmacokinetic (parameter)-pharmacodynamic (efficacy and toxicity) relationships of ganciclovir. The overall impact of such studies should contribute significantly to the more efficacious and safe use of ganciclovir.

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